Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin

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ORIGINAL INVESTIGATIONS

Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin

ROCKET AF Trial

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ABSTRACT

BACKGROUND Gastrointestinal (GI) bleeding is a common complication of oral anticoagulation.

OBJECTIVES This study evaluated GI bleeding in patients who received at least 1 dose of the study drug in the on-treatment arm of the ROCKET AF (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial.

METHODS The primary outcome was adjudicated GI bleeding reported from first to last drug dose + 2 days. Multivariable modeling was performed with pre-specified candidate predictors.

RESULTS Of 14,236 patients, 684 experienced GI bleeding during follow-up. These patients were older (median age 75 years vs. 73 years) and less often female. GI bleeding events occurred in the upper GI tract (48%), lower GI tract (23%), and rectum (29%) without differences between treatment arms. There was a significantly higher rate of major or nonmajor clinical GI bleeding in rivaroxaban- versus warfarin-treated patients (3.61 events/100 patient-years vs. 2.60 events/100 patient-years; hazard ratio: 1.42; 95% confidence interval: 1.22 to 1.66). Severe GI bleeding rates were similar between treatment arms (0.47 events/100 patient-years vs. 0.41 events/100 patient-years; $p = 0.39$; 0.01 events/100 patient-years vs. 0.04 events/100 patient-years; $p = 0.15$, respectively), and fatal GI bleeding events were rare (0.01 events/100 patient-years vs. 0.04 events/100 patient-years; 1 fatal events vs. 5 fatal events total). Independent clinical factors most strongly associated with GI bleeding were baseline anemia, history of GI bleeding, and long-term aspirin use.

CONCLUSIONS In the ROCKET AF trial, rivaroxaban increased GI bleeding compared with warfarin. The absolute fatality rate from GI bleeding was low and similar in both treatment arms. Our results further illustrate the need for minimizing modifiable risk factors for GI bleeding in patients on oral anticoagulation. (J Am Coll Cardiol 2015;66:2271–81)

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

GI = gastrointestinal

INR = international normalized ratio

NA = North America

NOAC = non-VKA oral anticoagulants

NSAID = nonsteroidal anti-inflammatory drug

OAC = oral anticoagulant

PPI = proton pump inhibitor

PRBC = packed red blood cell

ROW = rest of the world

TTR = therapeutic time in range

VKA = vitamin K antagonist

Gastrointestinal (GI) bleeding is a common complication of oral anticoagulant (OAC) therapy that occurs in 1% to 3% of patients on long-term OAC therapy (1). Established risk factors for GI bleeding in patients who receive vitamin K antagonists (VKAs) include previous GI bleeding, age, comorbid conditions, intensity of anticoagulation therapy, and concomitant medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] and antiplatelet agents) (2). However, the incidence and risk factors for GI bleeding have not been well studied in patients who take non-VKA oral anticoagulants (NOACs). Management of OAC in the setting of GI bleeding is controversial, and the optimal strategy has not yet been established (2,3).

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The ROCKET AF (Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study was a randomized controlled trial of rivaroxaban versus warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF) who were at moderate to high risk for stroke (4). ROCKET AF demonstrated that rivaroxaban was noninferior to warfarin for the prevention of stroke and systemic embolism (5), and rates of major and nonmajor clinically relevant bleeding were similar between treatment arms in the study. Patients randomized to rivaroxaban had fewer intracranial hemorrhages compared with warfarin, but they had significantly more GI bleeding (6). The objectives of this retrospective analysis were to investigate the incidence and severity of GI bleeding, the factors associated with GI bleeding, and antithrombotic management of GI bleeding in the ROCKET AF trial.

METHODS

The ROCKET AF trial design and primary results have been previously published (4,5). Briefly, ROCKET AF was a double-blind, double-dummy, international noninferiority trial that compared once-daily rivaroxaban versus dose-adjusted warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular AF. Patients had to have previous stroke or transient ischemic attack or ≥2 risk factors for stroke. Patients with only 2 risk factors were capped at 10% of the overall trial population, although the observed proportion of these patients in the trial was 13%. The primary endpoint was stroke or noncentral nervous system embolism. Patients were monitored no less than once every 4 weeks.

STUDY POPULATION. We included all patients in the on-treatment (or "safety") population of the ROCKET AF trial, which included those who were randomized and received at least 1 dose of the study drug.

OUTCOMES. The primary safety outcomes for the ROCKET AF trial were major and nonmajor clinically relevant bleeding. In this study, we focused on adjudicated GI bleeding reported during the safety period (from first drug dose to last dose + 2 days). All bleeds were adjudicated by a multispecialty clinical events committee blinded to the patients' treatment assignments. GI bleeding events included upper GI, lower GI, and rectal bleeding. GI bleeding was further categorized by event classification: the composite principal safety endpoint (major or nonmajor clinically relevant bleeding); major bleeding; major bleeding with a hemoglobin drop of ≥2 g/dl; major bleeding with transfusion; major bleeding with

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transfusion of ≥4 U of whole blood or packed red blood cells (PRBCs); major bleeding that was fatal; and nonmajor clinically relevant bleeding.

In the outcomes analyses, only the first GI bleed of each type for each patient was considered. For summaries of drug discontinuation and resumption, only the last GI bleed of any kind for each patient was considered. Permanent discontinuation of study drug was defined as the last dose received on the day of, or 1 or 2 days after, the patient's last GI bleed. Patients who died within this timeframe were not considered discontinuations. All events that occurred while patients received the study drug until 2 days after the last dose of the study drug were included in the analyses. Fatal bleeding events were those that resulted in death within 30 days of a qualifying bleeding event.

STATISTICAL METHODS. Multivariable modeling to identify baseline characteristics associated with major or nonmajor clinically relevant GI bleeding was performed with candidate predictors, including age, sex, diastolic blood pressure, estimated glomerular filtration rate (Cockcroft-Gault), previous GI bleed, anemia, hypertension, diabetes, current or former smoker, chronic obstructive pulmonary disease, sleep apnea; previous long-term aspirin use, previous antiplatelet use, and baseline use of NSAIDs, proton pump inhibitors (PPIs), or H2 antagonists. These variables were chosen based upon previous literature that indicated them as likely factors associated with GI bleeding (7). Continuous candidate predictors were first assessed for the linearity of their relationship with GI bleeding, using restricted cubic splines, and modifications (e.g., splines or truncations) made as necessary.

Candidate predictors were then entered into a Cox proportional hazards model, and forward stepwise selection was used to select independent predictors. Randomized treatment was forced into the model, and interaction was tested to determine whether predictors would differ depending on treatment assignment. Although the selection procedure included only patients with complete data for all candidate predictors, the final model included all patients with complete data for the selected predictors. International normalized ratio (INR) values were entered as a time-dependent covariate by using, at each event time, the mean of each patient's INR values from the previous 4 weeks. For event times earlier than 4 weeks, the mean of available previous INR values was used. INR values included all values imputed by the Rosendaal method as part of the time in therapeutic range (TTR) calculation. The proportional hazards assumption was checked for all final predictors and found to have been met.

For assessing the association of randomized treatment with GI bleeding outcomes, Cox proportional hazards models were used that included randomized treatment and all of the predictors identified previously. The proportional hazards assumption was checked for randomized treatment in all models and found to have been met. Due to differing length of follow-up among patients, event rates are presented as events per 100 patient-years.

Geographic variation was evaluated because of previous data on differences in TTR. The cohort was divided into North America (NA) and rest of world (ROW), and GI bleeding event rates, adjusted hazard ratios (HRs), and statistical interaction were all calculated for these groups. The previously described GI bleeding model was used, with region replaced by the dichotomous NA and/or ROW variable, and a term for the interaction between NA and/or ROW and randomized treatment added. Sensitivity analyses were also performed for all bleeding events in these cohorts. All statistical analyses of the aggregate, de-identified data were performed by the Duke Clinical Research Institute using SAS software (version 9.2, SAS Institute, Cary, North Carolina).

RESULTS

POPULATION CHARACTERISTICS. Of the 14,236 patients enrolled in ROCKET AF, 684 (290 warfarin [42%] and 394 [58%] rivaroxaban) had major and nonmajor clinically relevant GI bleeds during follow-up (**Table 1**). Compared with patients who did not have GI bleeding, patients with GI bleeding were less often female, slightly older (median age of 75 years), and more likely to have used VKAs previously. There was greater prevalence of renal insufficiency, diabetes, and hypertension in the GI bleeding population, but these patients less often had a history of thromboembolic events. Patients with GI bleeding in the trial were more likely to have had a history of GI bleeding, and there was an increased prevalence of sleep apnea, chronic obstructive pulmonary disease, and history of cigarette smoking in the GI bleeding group compared with patients without GI bleeding. The mean $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were similar in patients with and without GI bleeding. The pre-randomization use of aspirin or NSAIDs was more common in patients with GI bleeding. The use of PPIs and H2 antagonists was also higher among patients with GI bleeding compared with those without GI bleeding. For patients who

TABLE 1 Baseline Characteristics

	All Safety Patients (N = 14,236)	GI Bleed (n = 684)	No GI Bleed (n = 13,552)
Age, yrs	73 (65, 78)	75 (68, 79)	73 (65, 78)
Female	5,645 (40)	223 (33)	5,422 (40)
Type of AF			
Persistent	11,525 (81)	570 (83)	10,955 (81)
Paroxysmal	2,511 (18)	106 (15)	2,405 (18)
New onset	200 (1)	8 (1)	192 (1)
$CHADS_2$ score	3.5 ± 0.9	3.4 ± 0.9	3.5 ± 0.9
1	3 (<1)	0	3 (<1)
2	1,855 (13)	101 (15)	1,754 (13)
3	6,203 (44)	293 (43)	5,910 (44)
4	4,085 (29)	190 (28)	3,895 (29)
5	1,809 (13)	89 (13)	1,720 (13)
6	281 (2)	11 (2)	270 (2)
CHA_2DS_2-VASc score	4.9 ± 1.3	4.9 ± 1.3	4.9 ± 1.3
1	2 (<1)	0	2 (<1)
2	396 (3)	13 (2)	383 (3)
3	1,711 (12)	86 (13)	1,625 (12)
4	3,640 (26)	169 (25)	3,471 (26)
5	4,238 (30)	202 (30)	4,036 (30)
6	2,678 (19)	140 (20)	2,538 (19)
7	1,172 (8)	59 (9)	1,113 (8)
8	353 (2)	12 (2)	341 (3)
9	44 (<1)	3 (<1)	41 (<1)
HAS-BLED score	2.8 ± 0.9	2.9 ± 0.9	2.8 ± 0.9
0	91 (1)	1 (<1)	90 (1)
1	979 (7)	30 (4)	949 (7)
2	4,258 (30)	180 (26)	4,078 (30)
≥3	8,894 (62)	472 (69)	8,422 (62)
Presenting characteristics			
BMI, kg/m^2	28 (25, 32)	29 (26, 33)	28 (25, 32)
Systolic BP, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP, mm Hg	80 (70, 85)	78 (70, 83)	80 (70, 85)
Creatinine clearance,* ml/min	67 (52, 87)	65 (49, 84)	67 (52, 87)
Baseline comorbidities			
Previous GI bleed	499 (4)	64 (9)	435 (3)
Previous stroke, TIA, systemic embolism	7,794 (55)	311 (45)	7,483 (55)
Congestive HF	8,894 (62)	417 (61)	8,477 (63)
Hypertension	12,887 (91)	634 (93)	12,253 (90)
Diabetes	5,683 (40)	298 (44)	5,385 (40)
Previous MI	2,460 (17)	143 (21)	2,317 (17)
PAD	836 (6)	57 (8)	779 (6)
COPD	1,493 (10)	112 (16)	1,381 (10)
Current or former smoker	4,781 (34)	311 (45)	4,470 (33)
Stopped >1 yr ago	3,589 (25)	244 (36)	3,345 (25)
Liver disease	746 (5)	42 (6)	704 (5)
Sleep apnea	645 (5)	61 (9)	584 (4)
Anemia	1,976 (14)	167 (25)	1,809 (14)

Continued on the next page

experienced GI bleeding during trial follow-up, the baseline clinical characteristics were similar between treatment arms (Online Table 1).

GI bleeding events were distributed in the following frequencies: 48% in the upper GI tract, 23% in the lower GI tract, and 29% in rectal locations. These frequencies were similar between warfarin- and rivaroxaban-treated patients (Table 2).

OUTCOMES. There were significantly more GI bleeding events in rivaroxaban-treated patients versus warfarin-treated patients (3.61 events/100 patient-years vs. 2.60 events/100 patient-years; HR: 1.42; 95% confidence interval [CI]: 1.22 to 1.66) (Figure 1). When separated by clinical severity, there were more major and nonmajor clinically relevant GI bleeding events in rivaroxaban-treated patients (Table 3). For the most severe bleeds, patients who required ≥4 U of whole blood or PRBC transfusion, and events that were fatal, there was a numerical balance between treatment groups with no statistically significant difference detected. There was a very low absolute rate of fatal GI bleeding, which occurred in 1 patient who received rivaroxaban and 5 patients who received warfarin. The proportion of patients who experienced fatal or severe GI bleeding that required ≥4 U of RBCs was low and also similar between rivaroxaban- and warfarin-treated patients (Central Illustration).

After multivariable adjustment for clinical characteristics, patients who received rivaroxaban had a significantly higher hazard for both major and nonmajor clinically relevant GI bleeding compared with patients who received warfarin. This extended to the subgroups of major bleeding, including GI bleeds that involved a hemoglobin drop of ≥2 g/dl, and GI bleeds that required transfusion, but this was not significant for fatal GI bleeds or in those who required ≥4 U of RBC transfusion (Table 3).

STUDY DRUG AND ANTIPLATELET THERAPY MANAGEMENT IN THE SETTING OF GI BLEEDING. The decision to re-start or permanently withdraw the study drug after resolution of a bleeding event was left to the discretion of the investigator according to local practice. In the setting of GI bleeding, 34% of patients remained on the study drug (21.1% of major, 47.9% of nonmajor clinically relevant bleeding), whereas 27% permanently discontinued the study drug either at the time of bleeding or 1 to 2 days previously (Table 4). Patients with major GI bleeding had higher rates of permanent discontinuation compared with those with nonmajor clinically relevant GI bleeding (27.6% vs. 10.7%). A total of 39% of patients stopped the study drug at or near the time of GI bleed and re-started the study drug afterward, with a median duration of interruption of 9 days. There was a similar frequency of study drug re-start in patients with major versus nonmajor clinically relevant GI bleeding (38.5% vs. 39.6%), although the median duration of interruption was shorter in

patients with nonmajor clinically relevant GI bleeding (16 vs. 7 days). Of patients who had a GI bleed, 37.8% were on aspirin before their event, whereas 15.5% were on another antiplatelet agent before their event. Nearly one-half of these patients remained on antiplatelet therapy during their GI bleed, whereas the remaining patients stopped antiplatelet agent use, and the majority of these patients stopped taking this therapy permanently. Patterns of discontinuation of aspirin and antiplatelet agents were similar for major and nonmajor clinically relevant GI bleeding and were also similar across treatment groups (Online Tables 2 and 3).

FACTORS ASSOCIATED WITH GI BLEEDING. As shown in **Table 5**, multivariable modeling was used to identify clinical factors associated with GI bleeding. The factors most strongly associated with GI bleeding were anemia at baseline, a history of GI bleeding, long-term aspirin use, and rivaroxaban use (vs. warfarin use). Other significant clinical factors associated with bleeding included increasing age, smoking, diastolic blood pressure, history of PPI use, history of obstructive sleep apnea, and decreasing creatinine clearance. There was no interaction between predictors of GI bleeding and treatment assignment ($p = 0.73$ for interaction). Detailed information on event rates for each of these subgroups can be found in Online Table 4. Cubic spline plots, generated to evaluate the effect of INR values on GI bleeding, showed an inflection point at an INR of 2.0 (**Figure 2**). For every 1 U of increase in INR for values <2.0, there was significantly less hazard for bleeding. For every 1 U of increase >2.0, there was significantly more hazard for major and nonmajor clinically relevant GI bleeding.

GEOGRAPHIC VARIATION. When the study cohort was divided into NA and ROW groups, there were significantly greater rates of TTR in NA patients compared with those from the ROW (65.5 vs. 55.7; $p < 0.001$). NA patients also had significantly higher rates of GI bleeding in both treatment arms compared with the ROW patients (**Table 6**). After adjustment for clinical risk factors, including concomitant antiplatelet medications, patients in NA who received rivaroxaban had a significantly higher hazard for GI bleeding than those on warfarin (p for interaction = 0.0069). There were also greater rates of overall bleeding in NA versus ROW patients, but no statistically significant interaction was found between geographic location and treatment assignment for overall bleeding (Online Table 5). The anatomic location of GI bleeding was significantly different between NA and ROW patients, with a substantially greater proportion of GI bleeds in NA stemming from a lower GI location (30% vs. 19%) and substantially fewer GI bleeds proportionally from an upper GI location (38% vs. 53%) compared with ROW patients (Online Table 6). Use of antiplatelet agents was similar among patients from NA compared with ROW, both at baseline (37% vs. 40%) and during follow-up (42% vs. 43%) (Online Table 7).

TABLE 1 Continued

	All Safety Patients (N = 14,236)	GI Bleed (n = 684)	No GI Bleed (n = 13,552)
Medications			
Previous VKA use	8,889 (62)	459 (67)	8,430 (62)
Previous long-term ASA use	5,194 (36)	291 (43)	4,903 (36)
NSAID use at baseline	507 (4)	35 (5)	472 (3)
PPI use at baseline	1,807 (13)	143 (21)	1,664 (12)
H2 antagonist use at baseline	311 (2)	23 (3)	288 (2)
Antiplatelet (other than ASA) at baseline	409 (3)	28 (4)	381 (3)
Randomized to rivaroxaban	7,111 (50)	394 (58)	6,717 (50)

Values are median (25th, 75th percentiles), n (%), or mean ± SD. *Calculated using the Cockcroft-Gault equation.

AF = atrial fibrillation; ASA = aspirin; BMI = body mass index; BP = blood pressure; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism – vascular disease, age 65–74 years, sex category; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA; COPD = chronic obstructive pulmonary disorder; GI = gastrointestinal; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; HF = heart failure; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral artery disease; PPI = proton-pump inhibitor; TIA = transient ischemic attack; VKA = vitamin K antagonist.

DISCUSSION

In a large, contemporary trial of moderate- to high-risk patients with nonvalvular AF who received OAC, rivaroxaban increased the rates of both major and nonmajor clinically relevant GI bleeding compared with warfarin (**Central Illustration**). Rates of the most severe GI bleeding, including those that were fatal and in patients who required ≥4-U RBC transfusion, were very low and similar between rivaroxaban- and warfarin-treated patients. Factors associated with GI bleeding in patients on warfarin or rivaroxaban were similar to previously established risk factors for GI

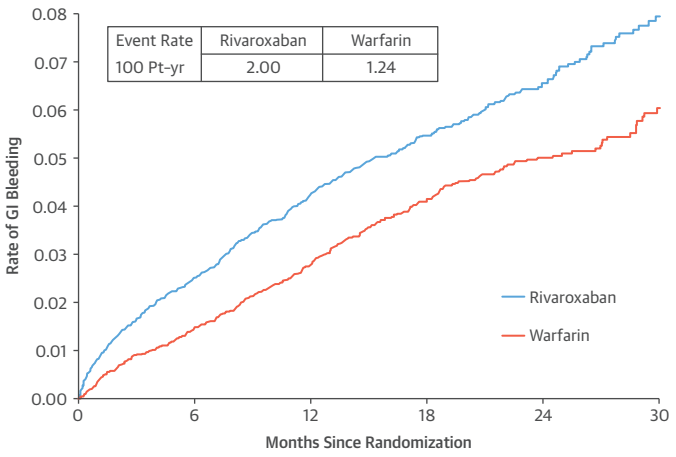
TABLE 2 Anatomical Locations of GI Bleeding Events

GI Bleed Location	All With GI Bleeds (n = 684)	Rivaroxaban (n = 394)	Warfarin (n = 290)
Upper (hematemesis or melena)	328 (48)	190 (48)	138 (47)
Lower	156 (23)	87 (22)	69 (24)
Rectal	200 (29)	117 (30)	83 (29)

Values are n (%).

GI = gastrointestinal.

FIGURE 1 Kaplan-Meier Curve of Time to First Major GI Bleeding Event by Treatment Arm



Rivaroxaban-treated patients had a significantly shorter time to their first major gastrointestinal (GI) bleeding event compared with warfarin-treated patients during follow-up in the ROCKET AF trial.

bleeding. These results highlight a small but definite risk for GI bleeding that might be attenuated by minimizing concomitant risk factors.

RISK OF GI BLEEDING WITH NOAC. NOACs have been associated with increased risk of GI bleeding across several trials (6). This is in contrast to 2 recent clinical registry analyses. Abraham et al. (8) and Chang et al. (9), who both performed large U.S. claims-based registry analyses and used propensity-matched comparisons, showed that the risk of GI bleeding was similar in patients who took dabigatran or rivaroxaban compared with those who took warfarin. When the results of all 4 clinical trials of NOAC efficacy in AF were pooled in a recent meta-analysis from published reports and not patient-level data (10), the NOACs, evaluated together, showed similar rates of major bleeding compared with warfarin, but also had an overall slightly increased risk for GI bleeding (HR: 1.25; 95% CI: 1.01 to 1.55; $p = 0.04$), with significant heterogeneity of effect ($I^2 > 70\%$). The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (11), which was a randomized, open-label study of dabigatran versus dose-adjusted warfarin for the prevention of stroke, showed similar results (12). There was an excess of GI bleeding (1.85% vs. 1.25%; $p < 0.001$) in patients on the 150 mg, twice-daily dose of dabigatran compared with those on dose-adjusted warfarin. The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) trial also showed an excess of GI bleeding (1.51% vs. 1.23%; $p = 0.03$) in patients who received 60 mg of edoxaban versus dose-adjusted warfarin (13). Alternatively, the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial showed similar rates of GI bleeding (0.76% vs. 0.86%; $p = 0.37$) in apixaban- versus warfarin-treated patients (14). Thus, apixaban seems to be unique among the currently approved NOAC agents with regard to GI bleeding events. This is consistent with the overall safety profile of apixaban seen in the ARISTOTLE trial, because it exhibited a reduced risk for major and nonmajor clinically relevant bleeding compared with warfarin. Despite the increased risk of GI bleeding with rivaroxaban in our study, there were very few fatal events in either treatment arm. In the RE-LY and ENGAGE AF-TIMI 48 trials, rates of fatal bleeding were also significantly lower with dabigatran and edoxaban compared with warfarin, but data on the severity of GI bleeding are not yet available. Our study provides the first in-depth analysis of a NOAC across the GI bleeding risk spectrum. It also provides evidence that there is an increased risk of GI bleeding with rivaroxaban, but

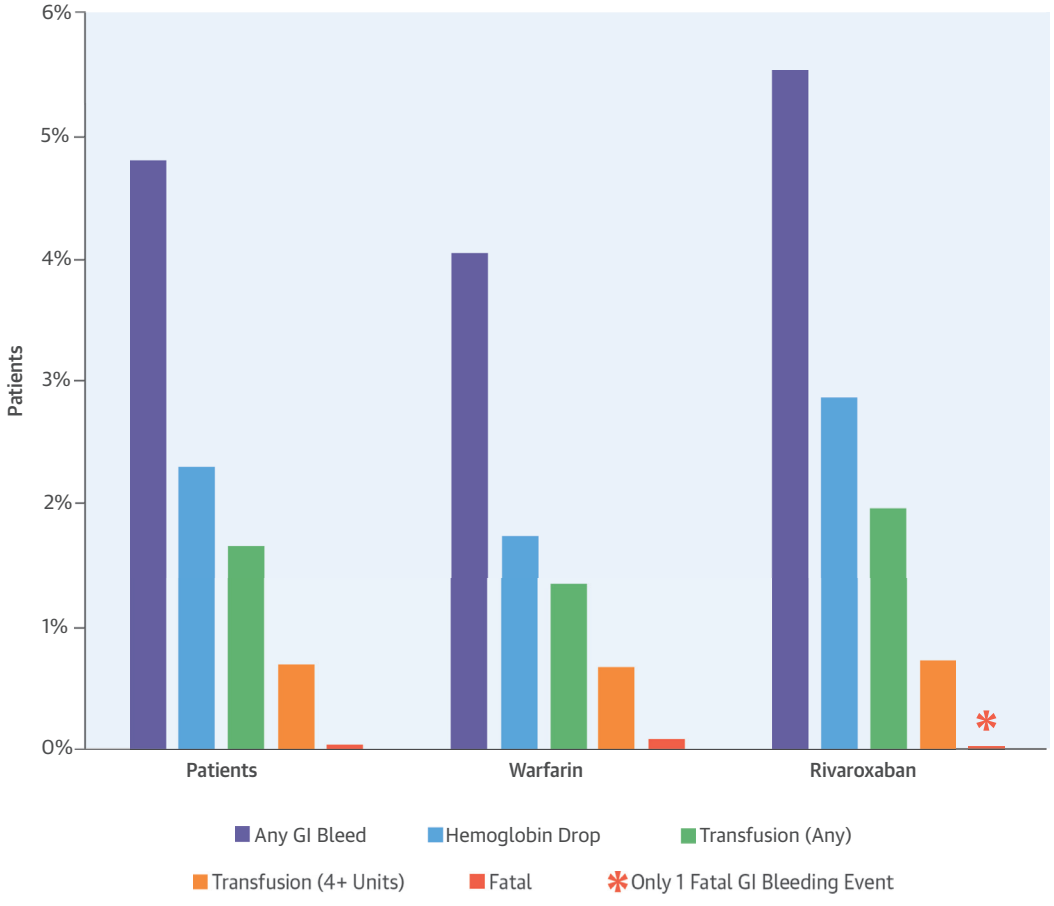
TABLE 3 Overall Rates of GI Bleeding by Treatment Arm

Outcomes	Rivaroxaban (n = 7,111) Events/100 Patient-Years (Total Events)	Warfarin (n = 7,125) Events 100/Patient-Years (Total Events)	Rivaroxaban vs. Warfarin Adjusted HR (95% CI)*	p Value
Major or NMCR bleeding	3.61 (394)	2.60 (290)	1.42 (1.22–1.66)	<0.0001
Major bleeding	2.00 (221)	1.24 (140)	1.66 (1.34–2.05)	<0.0001
Hemoglobin drop ≥2 g/dl	1.84 (204)	1.11 (125)	1.69 (1.35–2.12)	<0.0001
Transfusion	1.27 (141)	0.85 (96)	1.56 (1.20–2.02)	0.0010
Transfusion ≥4 U	0.47 (52)	0.41 (47)	1.19 (0.80–1.77)	0.39
Fatal	0.01 (1)	0.04 (5)	0.21 (0.02–1.76)	0.15
NMCR	1.75 (193)	1.39 (156)	1.28 (1.43–1.59)	0.023

*Hazard ratios (HRs) and p values are from Cox proportional hazards models that include randomized treatment and all identified predictors of major or nonmajor clinical bleeding (NMCR) GI bleeding (Table 5).

CI = confidence interval; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION **GI Bleeding in ROCKET AF Trial: Histogram of the Distribution of GI Bleeding Stratified by Treatment Arm**



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Rivaroxaban-treated patients had higher rates of major and minor gastrointestinal (GI) bleeding events compared with warfarin-treated patients; however, rates of the most severe GI bleeding events, including those that required transfusion of packed red blood cells and those that resulted in death, were comparable between treatment groups.

similar, extremely low rates of fatal GI bleeding with warfarin and rivaroxaban.

MECHANISM OF GI BLEEDING WITH NOAC. The possible mechanisms by which rivaroxaban, dabigatran, and edoxaban are associated with a greater risk of GI bleeding are not well understood. Dabigatran and the factor Xa inhibitors, to a lesser degree, all have partial elimination through the gut and are substrates of the P-glycoprotein transport system (15). This system actively pumps drugs into the GI tract, allowing for greater concentrations of the active agent to remain in the gut. Dabigatran has limited bioavailability (7.2%) and is directly activated in the GI tract, which allows for prolonged exposure to an active anticoagulant compound. It also has tartaric acid in the compound, which is thought to contribute to dyspepsia. In this scenario, surface lesions in the GI tract, with prolonged exposure to an active anticoagulant compound, may be more likely to bleed. In comparison, warfarin has extremely high bioavailability and is absorbed fully from the gut, because the unabsorbed form of warfarin is inactive (16). Although this may explain the differential GI bleeding risk seen with dabigatran compared with warfarin, it does not explain the differential GI bleeding risk seen between the factor Xa agents.

TABLE 4 Study Drug, Antiplatelet Therapy Use Relative to GI Bleed Events

Medical Therapy	All Patients With GI Bleeds (N = 679)	Major Bleeding (n = 351)	NMCR Bleeding (n = 328)
Study drug			
Remained on study drug at time of bleed	231 (34.0)	74 (21.1)	157 (47.9)
Stopped before or at time of bleed and resumed later	265 (39.0)	135 (38.5)	130 (39.6)
Permanently discontinued at time of bleed	132 (19.4)	97 (27.6)	35 (10.7)
Had permanently discontinued 1 or 2 days before bleed	51 (7.5)	45 (12.8)	6 (1.8)
Number of days to resumption of study drug from bleed	9 (4, 25)	16 (6, 30)	7 (3, 14)
ASA			
Received at any time post-randomization and before bleed	257 (37.8)	147 (41.9)	110 (33.5)
Remained on ASA at time of bleed	153 (22.5)	88 (25.1)	65 (19.8)
Stopped before or at time of bleed	104 (15.3)	59 (16.8)	45 (13.7)
Resumed ASA after bleed (within 90 days)	6 (0.9)	5 (1.4)	1 (0.3)
Days to resumption of ASA from bleed	15 (13, 16)	14 (13, 16)	15
Antiplatelet agent (not including ASA)			
Received at any time post-randomization and before bleed	105 (15.5)	57 (16.2)	48 (14.6)
Remained on antiplatelet at time of bleed	47 (6.9)	24 (6.8)	23 (7.0)
Stopped before or at time of bleed	58 (8.5)	33 (9.4)	25 (7.6)
Resumed antiplatelet after bleed (within 90 days)	4 (0.6)	4 (1.1)	–
Days to resumption of antiplatelet from bleed	55 (26, 69)	55 (26, 69)	–

Values are n (%) or median (25th, 75th percentiles).
Abbreviations as in Tables 1 and 2.

Apixaban, rivaroxaban, and edoxaban all have >50% bioavailability; therefore, the less active compound is allowed to pass through the gut. The elevated GI bleeding rates seen with rivaroxaban and edoxaban may be due to differential dose and pharmacokinetics of these drugs compared with apixaban. Further investigation is necessary to understand this phenomenon.

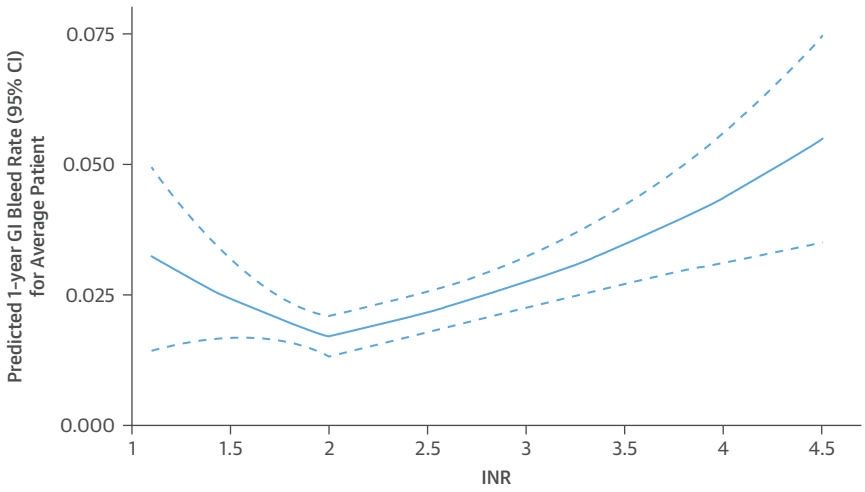
RISK FACTOR MODIFICATION FOR GI BLEEDING. For patients with AF, risk stratification is a critical step in management. Current guidelines emphasize the use of thrombotic risk scores and shared decision making with patients, carefully considering stroke and bleeding risks (17). The use of bleeding risk scores has also been recommended, but may not affect therapeutic choices in the same way. Bleeding risk scores often reflect high thrombotic risk as well; thus, correction of modifiable risk factors before OAC would be a prudent strategy rather than withholding OAC (7). In a recent analysis of net clinical benefit in a large national cohort, Olesen et al. (3) found that VKA use alone was beneficial, regardless of bleeding risk. In our study, there was no observed difference in the bleeding risk score (HAS-BLED) or thrombotic risk score ($CHADS_2$, CHA_2DS_2-VASc) for patients with GI bleeding versus without GI bleeding. Several independent factors for GI bleeding identified in our study, particularly previous GI bleeding, age, decreasing creatinine clearance, and anemia at baseline, agree with previously validated score-based risk factors for bleeding (18). Potentially modifiable risk factors identified in our study included the concomitant use of aspirin and other antiplatelet agents, which are known risk factors for GI bleeding. A recent ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) analysis showed that aspirin: 1) is often used in patients on OAC who do not have a clear indication for long-term antiplatelet therapy; and 2) significantly increases the risk for bleeding events (19). In the aforementioned net

TABLE 5 Predictors of GI Bleeding (Major or NMCR)

	Wald Chi-Square	HR (95% CI)	p Value
Anemia at baseline	31.9	1.70 (1.41–2.04)	<0.0001
Previous GI bleed	30.2	2.11 (1.62–2.76)	<0.0001
Long-term ASA use at screening	23.5	1.47 (1.26–1.72)	<0.0001
Rivaroxaban vs. warfarin	20.1	1.42 (1.22–1.66)	<0.0001
Age (for each 5-yr increase)	18.2	1.11 (1.06–1.17)	<0.0001
Diastolic BP (for each 5 mm Hg decrease to <80 mm Hg)	13.8	1.10 (1.05–1.16)	0.0002
Smoking history (current or former)	13.6	1.37 (1.16–1.62)	0.0002
History of sleep apnea	11.6	1.60 (1.22–2.10)	0.0007
PPI at baseline	9.7	1.36 (1.12–1.65)	0.0018
Creatinine clearance (for each 5-U decrease to <60 ml/min)	6.0	1.06 (1.01–1.12)	0.015
COPD	5.8	1.30 (1.05–1.61)	0.016
Male	4.4	1.21 (1.01–1.44)	0.037
Baseline antiplatelet (other than ASA)	4.3	1.50 (1.02–2.21)	0.039

Abbreviations as in Tables 1 and 3.

FIGURE 2 Predicted 1-Year Event Rate (With Point-Wise 95% CI) for the "Average" Patient



On multivariable modeling, predicted 1-year GI bleeding event rates were lowest for patients with average international normalized ratio (INR) values of 2.0, with incremental increased risk for each INR unit above and below 2.0. Average values for all other covariates shown for the range of 1st to 99th percentiles of INR distribution. CI = confidence interval; GI = gastrointestinal.

clinical benefit analysis, concomitant aspirin and VKA use increased bleeding risk without substantially decreasing the risk of stroke compared with VKA use alone (3). Reducing exposure to modifiable risk factors such as concomitant medications is essential to optimizing the risk and/or benefit balance, and is currently recommended by international AF practice guidelines (20,21).

Another possible modifiable risk factor for patients on VKA agents is the maintenance of INR value in the therapeutic range. Our data indicate that INR values both substantially below and above 2.0 contributed to the risk of major and nonmajor clinically relevant GI bleeding. Although it may be counterintuitive that lower INR values would also increase GI bleeding risk, we believe that this serves as a surrogate marker (like TTR) of medication nonadherence or comorbid illness that would increase bleeding risk. INR variability has been studied by Razouki et al. (22), who found that high INR variability (regardless of results above or below our clinical thresholds) was independently associated with both adverse thrombotic and bleeding events. This was supported in a separate study by Lind et al. (23), who also measured INR variability and came to similar conclusions, that high variability is independently associated with higher rates of all-cause mortality, stroke, bleeding, and hospitalization. Thus, it remains imperative for patients on VKAs to carefully monitor INR values to reduce risk for both stroke and bleeding.

The association of PPI use with GI bleeding is likely confounded by indication. Patients with a history of GI bleeding, or perhaps with GI pathology and/or symptoms, are at a higher risk for GI bleeding, but are often administered PPI therapy as treatment. PPI use is more frequent in patients who have had GI bleeding or are at risk, but PPIs are unlikely to have a causal association with GI bleeding. Our results indicate previously validated GI bleeding risk factors may have utility in a contemporary population of patients taking a NOAC. There was no interaction between treatment assignment and predictors of GI bleeding; thus, the risk predictors found in our study would have utility in both warfarin- and rivaroxaban-treated patients. However, there are few treatment

TABLE 6 Geographic Variation in GI Bleeding Rates and Treatment Effect

Geographic Location	Treatment	GI Bleeding Events per 100 Patient-Years (Total Events)	HR (95% CI) Rivaroxaban vs. Warfarin	p Value
NA	Rivaroxaban	7.13 (156)	1.89 (1.45–2.45)	<0.001
	Warfarin	3.83 (90)		
Rest of world	Rivaroxaban	2.73 (238)	1.21 (1.00–1.47)	0.047
	Warfarin	2.27 (200)		
Interaction NA × rivaroxaban	—	—	—	0.0069

NA = North America; other abbreviations as in Tables 1 and 3.

strategy data that indicate what level of GI bleeding risk would nullify the benefits of OAC for stroke prevention in appropriate patients with AF (3,7). There are no data available for NOACs in this challenging situation (24), but the rates of discontinuation of OAC, even in the setting of nonmajor clinically relevant bleeding, were high in our study. The interplay of bleeding risk factors with thrombotic risk factors creates a challenging situation for clinicians. Further investigation is necessary to provide adequate anticoagulation strategies for complex patients with thrombotic risk and risk for GI bleeding.

Geographic variation in GI bleeding rates and hazards was seen in our study population, even after multivariable adjustment for differences in clinical risk factors and differential use of antiplatelet agents. This is not easily explained, but there was more overall bleeding seen in NA versus ROW patients. In addition, the anatomic location of bleeding was more often in the lower GI tract in NA than in the ROW. This may be due to disparate practice patterns and more aggressive screening for anemia and lower GI malignancy in NA compared with other geographic regions, which may partly explain the higher reported rates of bleeding.

STUDY LIMITATIONS. First, this was a post-hoc, nonrandomized, subgroup analysis of the ROCKET AF trial. As such, the study was not powered for comparison of clinical outcomes in the GI bleeding population of the trial. Also, we had only limited data on management of the GI bleeds. Finally, inclusion and exclusion criteria for the ROCKET AF trial created a select population of moderate- to high-risk patients; thus, findings for GI bleeding risk may not be generalizable to a broader population of patients.

CONCLUSIONS

In the ROCKET AF trial, both major and nonmajor clinically relevant GI bleeding events were more frequent in patients taking rivaroxaban compared with warfarin. The most severe bleeding events, such as those that required transfusion of ≥4 U of RBCs or those that caused death were balanced between treatment groups. The absolute fatality rate from GI bleeding events was very low in both treatment arms. Our results further highlight the importance of the risk and benefit consideration of OAC in patients at risk for GI bleeding and illustrate the need for minimizing modifiable risk factors for GI bleeds.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with AF and additional stroke risk factors, anticoagulation with rivaroxaban is associated with a higher rate of major or nonmajor clinically relevant GI bleeding than warfarin, but the rates of the most severe GI bleeding complications are similar with these agents.

TRANSLATIONAL OUTLOOK: Further studies are needed to establish the optimal stroke prevention strategy for patients with AF who face a high risk of bleeding complications during long-term anticoagulation.

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KEY WORDS anticoagulant, atrial fibrillation, gastrointestinal bleeding, hemorrhage, risk stratification

APPENDIX For supplemental tables, please see the online version of this article.